REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. Status Of The Claims And Formal Matters

Claims 1-21 are pending in this application. Claim 5 has been canceled without prejudice. Claims 1, 3, 9-11, 13 and 15 have been amended. No new matter has been added by this amendment.

Claims 1, 3, 13 and 15 have been clarified to recite a method for promoting cell death of a cell which has previously been exposed to a cytotoxic agent or irradiation. Claims 1, 3, 9 and 10 have been clarified to recite an inhibitor instead of a modulator. Claims 1 and 13 have been clarified to recite contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. Support for this recitation is found on page 8, paragraph 16; page 14, paragraph 34 and pages 16-17, paragraph 40 of the specification as originally filed. Claims 6, 9 and 11 have been clarified to depend from claim 1 instead of canceled claim 5.

New claims 33-52 are added. Support for the claims can be found in the specification, including the original claims as filed. New claim 33 recites the phrase "wherein the cytotoxic agent is not stored in acidic vesicular organelles of said cell," thereby distinguishing the cells of claim 33 from cells which sequester and store such agents acidic vesicular organelles. Support for this recitation can be found at least in the Examples, wherein the exemplified cells did not have a cytotoxic agent of the invention stored in acidic vesicular compartments when contacted with an inhibitor of vacuolar proton ATPase activity (see, for example, the cells of Tables 3-11). New claim 43 specifies the sequence of administration, as described on page 39 of the specification.

The Examiner is thanked for withdrawing the previous claim objections and 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103 rejections in the Office Action.

It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§ 101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the addition and amendments to the

claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. The Rejections Under 35 U.S.C. § 112, 2nd Paragraph, Are Overcome

Claims 1-21 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner contends that claim 1 is indefinite wherein the claim is draw to a "modulator" of vacuolar proton ATPase activity and requests clarity. Although Applicants do not agree with the Examiner, in the interest of expediting prosecution, claims 1, 3, 9 and 10 have been clarified to recite "inhibitor" instead of "modulator", thereby obviating the rejection. Since claims 2, 4 and 6-12 depend from claims 1 or 3, the rejection to claims 2, 4 and 6-12 have also been obviated.

The Examiner alleges that claims 1 and 13 are confusing wherein the claims read "a method for promoting cell death following exposure to a cytotoxic agent comprising" and suggests a recitation of "a method of promoting cell death of a cell which has previously been exposed to a cytotoxic agent comprising" to clearly articulate in the preamble that it is the cell which has been previously treated with a cytotoxic agent, and that this is also the cell which the method is to be practiced on. In the interest of expediting prosecution, claims 1, 3, 13 and 15 have been clarified to insert the Examiner's suggested recitation, thereby obviating the rejection. Since claims 2, 4, 6-12, 14 and 16-21 depend from claims 1, 3, 13 or 15, the rejection to claims 2, 4, 6-12, 14 and 16-21 have also been obviated.

It is believed that the rejections under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal are requested.

III. The Rejections Under 35 U.S.C. § 102 Are Overcome

Claims 1, 2, 4-8, 11-14 and 16-19 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Altan *et al.* (Document 18 of IDS submitted February 10, 2003, hereinafter "Altan"). The Examiner contends that Altan discloses that administering monensin, bafilomycin A1 or concanamycin to a cell which is resistant to adriamycin from previous therapies, sufficiently changes the cells to that of a drug-sensitive cell thereby rendering the cell vulnerable once again to chemotherapy. This rejection is respectfully traversed. This rejection is moot in

light of the amendments to the claims submitted herein. The cited reference does not anticipate the instant invention.

The instant invention, in part, relates to a method for promoting cell death of a cell which has previously been exposed to a cytotoxic agent comprising contacting said cell with (a) an inhibitor of vacuolar proton ATPase activity or (b) an agent capable of inhibiting acidic vesicular function or acification (e.g., an inhibitor of vacuolar proton ATPase activity) prior to an accumulation of acidic vesicular organelles in said cell.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention. Claims 1 and 13 have been clarified to recite contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. New claim 33 is directed to methods of the invention whereby treatment with the inhibitor of vacuolar proton ATPase activity is applied to cells not having a cytotoxic agent stored within internal acidic vesicular organelles of the cells.

Altan et al. showed that the acidic compartments in Adriamycin-resistant MCF-7 cells (MCF/ADR) are more acidic than their counterparts in MCF-7 drug-sensitive phenotypes. Consequently, MCF-7/ADR cells sequester weak base drugs, such as Adriamycin, into their acidic compartments. This discovery led to the hypothesis that sequestration of basic chemotherapy agents in acidic organelles constitutes a mechanism of drug resistance. Therefore, interference with acidification of the acidic compartments in drug-resistant cells will increase sensitivity to basic drugs by diverting them away from the acidic compartments and into the nucleus.

Altan does not teach or suggest contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. Altan does not teach or suggest

contacting a cell with an inhibitor prior to storage of a cytotoxic agent within acidic vesicular organelles of the cell. As stated in the previous response filed June 26, 2003, Altan relates to defective acification in drug-resistant cells. Altan relates to disrupting the acification of the organelles of resistant cells with monensin, bafilomycin A1 or concanamycin A to change the adriamycin distribution to that found in drug-sensitive cells, rending the cell vulnerable once again to chemotherapy (see, e.g., Summary of Altan). In other words, Altan illustrates the disruption of acidic organelles that have already formed within the cell and have already sequestered and stored a cytotoxic agent, thereby rendering the cell drug-resistant. As a result, Altan illustrates the conversion of drug resistant cells to non drug resistant cells with vacuolar proton ATPase inhibitors and observed a loss of acification within the vesicles (see, e.g., page 1594, left column, first two paragraphs of Altan).

In contrast, the presently claimed invention relates to non-drug resistant cells wherein acidic vesicular organelles have not yet accumulated within the cell and/or the cytotoxic agent is not stored in acidic vesicular organelles of the cell. The addition of (a) an inhibitor of vacuolar proton ATPase activity or (b) an agent capable of inhibiting acidic vesicular function or acification in the present invention prevents the formation and/or subsequent accumulation of acidic vesicular organelles. Altan strictly relates to the use of vacuolar proton ATPase inhibitors to disrupt the acidic vesicular organelles that have already formed within the cell and that have sequestered and stored a cytotoxic agent.

Since Altan does not teach or suggest contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell, or prior to storage of a cytotoxic agent in the cell, Altan does not contain each and every element of the claimed invention. It is submitted that the rejection of claims 1 and 13 have been obviated. Since claims 2, 4-8, 11, 12, 14 and 16-19 depend from claims 1 or 13, it is submitted that the rejections to claims 2, 4-8, 11, 12, 14 and 16-19 have also been obviated.

Consequently, reconsideration and withdrawal of the Section 102 rejections are earnestly requested.

IV. The Rejection Under 35 U.S.C. § 103 Is Overcome

Claims 9, 10, 20 and 21 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Altan in view of Boyd et al. (reference 1 of the IDS submitted February 10, 2003, hereinafter "Boyd"). This rejection is respectfully traversed. This rejection is moot in

light of the amendments to the claims submitted herein. The cited references do not make the instant invention obvious.

The Examiner alleges that Altan teaches the method of administering monensin, bafilomycin A1 or concanamycin to a cell which is resistant to adriamycin from previous therapies, sufficiently changes the cells to that of a drug-sensitive cell thereby rendering the cell vulnerable once again to chemotherapy but administration of a benzolactone enamide or salicilyhalamide A is not taught. The Examiner contends that Boyd teaches that benzolactone enamides, including salicilyhalamide A, are inhibitors of the growth of tumor cells as they inhibit vacuolar proton ATPase activity. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to administer a compound which has an art recognized activity (inhibit vacuolar proton ATPase activity) for another compound which has the same art recognized activity in a correlative method.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Claims 1 and 13 have been clarified to recite contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. As stated above, Altan does not teach or suggest contacting a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. There is no teaching, suggestion or motivation in Altan to contact a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell.

Boyd relates to the discovery of a novel class of benzolactone enamides and merely discloses that such benzolactone enamides selectively inhibit vacuolar proton ATPase activity. Boyd does not correct the deficiency of Altan because there is no teaching, suggestion or motivation in Boyd to contact a cell with an inhibitor prior to an accumulation of acidic vesicular

organelles in the cell. The combination of Altan and Boyd does not teach, suggest or motivate one of ordinary skill in the art to administer a benzolactone enamide or salicilyhalamide to promote cell death of a cell which has previously been exposed to a cytotoxic agent prior to an accumulation of acidic vesicular organelles in the cell.

It is submitted that the rejection of claims 9, 10, 20 and 21 has been obviated. Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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